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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,272	10/20/2001	Pranela Rameshwar	267/033	8309

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,272	RAMESHWAR, PRANELA	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *11-19, 23-27, 29, 31, 33-35, 37, 40, 42-43, 47, 50, 52, 55, 57, 59, 61-65, 68, 70, 72, 74-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-9,21 and 22* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are Claims 1-5, 7-9, 11-19, 21-27, 29, 31, 33-35, 37, 40, 42-43, 47, 50, 52, 55, 57, 59, 61-65, 68, 70, 72, and 74-77.

Rameshwar, Pranela
Date of Priority: 10/20/2000

DETAILED ACTION

Election/Restrictions

The Election filed on August 23, 2004 in response to the Restriction Requirement of June 28, 2004 is acknowledged and has been entered. Claims 6, 10, 20, 28, 30, 32, 36, 38, 39, 41, 44-46, 48, 49, 51, 53, 54, 56, 58, 60, 66, 67, 69, 71, and 73 have been cancelled. Claims 1-5, 7-9, 11-19, 21-27, 29, 31, 33-35, 37, 40, 42-43, 47, 50, 52, 55, 57, 59, 61-65, 68, 70, 72, and 74-77 are currently pending in the application. Claims 3, 34, 50, 63, and 77 have been amended to correct typographical errors.

Applicant's election with traverse of Group I, claims 1-10 and 21-22, as specifically drawn to an isolated polynucleotide comprising SEQ ID NO: 1, a vector, host cell and pharmaceutical composition has been acknowledged. The traversal is on the ground(s) that the claims set forth in the instant application relate to HGFIN molecules and methods or using the same. The Applicants believe that a search of the relevant prior art would reveal art related to HGFIN nucleic acids and proteins and method for using the same. Therefore, the applicants believe no additional burden would be incurred by the inclusion of all eighteen groups. The applicant further requests that if the restriction is maintained that claims 1-10 and 15-23 be searched and examined together for the following reasons. Polynucleotide comprising HGFIN sense and antisense nucleic acid sequences would be readily identified as the relevant prior art sequences pertaining to Groups I and IV would be revealed in a search of the nucleic acid sequence of SEQ ID NO: 1. These arguments have been considered and are not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the restriction requirement of June 28, 2004.

As to the question of burden of search, the inventions are classified differently, necessitating different searches of the US Patents and literature. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly

relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-77 are currently pending in the application.

Claims 6, 10, 20, 28, 30, 32, 36, 38, 39, 41, 44-46, 48, 49, 51, 53, 54, 56, 58, 60, 66, 67, 69, 71, and 73 have been cancelled

Claims 11-19, 23-27, 29, 31, 33-35, 37, 40, 42-43, 47, 50, 52, 55, 57, 59, 61-65, 68, 70, 72, 74-77 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-5, 7-9 and 21-22 are currently under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5 and 7, as written, do not sufficiently distinguish over host cells, as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught by page 50 of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21 and 22 are rejected as vague and indefinite for reciting "biologically effective amount" in claim 21. The phrase "biologically effective amount" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The term "substantially" in Claim 22 is a relative term, which renders the claim indefinite. The term "substantially" is not defined by the claim and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "substantially " could imply 50%, 60%, 70%, 80%, 90% or 99.9%.

Claims 3-5, 7-9, and 21 are rejected as vague and indefinite for reciting the term HGFIN in association with encoding characteristics as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify HGFIN, for example, by SEQ ID NO. and function of HGFIN.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7-9, and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of polynucleotides that have at least 70% identity to SEQ ID NO: 1 or to a genus of molecules referred to as "HGFIN. However,

the written description in this case only sets forth an HGFIN nucleotide sequence of SEQ ID NO: 1 that encodes the amino acid sequence SEQ ID NO: 2.

The specification teaches (page 34, paragraph 00102) that specific polynucleotides of the invention include, but are not limited to, isolated HGFIN polynucleotides that encode the HGFIN polypeptides and fragments, and polynucleotides closely related thereto. With regards to the HGFIN polynucleotide, the specification teaches (page 35, paragraphs 00102-00104) HGFIN polynucleotide not only includes the nucleotide sequence of SEQ ID NO: 1, but also any nucleotide sequence with at least 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 1. With regards to HGFIN polypeptide, the specification teaches (page 41, paragraph 0114) the HGFIN polypeptide relates to the not only human HGFIN (SEQ ID NO: 2) but any polypeptide that comprises an amino acid sequence with at least 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 2 over the entire length of SEQ ID NO: 2. However, the written description only reasonably conveys one species of a HGFIN polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1 that encodes one HGFIN polypeptide consisting of the amino acid sequence of SEQ ID NO: 2. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of SEQ ID NOs that encompass the genus of HGFIN polynucleotides that encode HGFIN polypeptide nor does it provide a description of structural features that are common to the polynucleotides. Further, the specification fails to provide a representative number of SEQ ID NOs that encompass the genus of HGFIN polypeptides along with a description of structural features that are common to the polypeptides. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species of HGFIN polynucleotides and

polypeptides is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of HGFIN polynucleotides and polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only an HGFIN polynucleotide (SEQ ID NO: 1) that encodes an HGFIN polypeptide (SEQ ID NO: 2), but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 21-22 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine

screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a pharmaceutical composition comprising a biological effective amount of a HGFIN polynucleotide and an acceptable carrier. Thus, the claims would imply a method of using the pharmaceutical composition comprised of a HGFIN polynucleotide for treating a disease.

The specification teaches (page 56, paragraph 0151) that a novel pharmaceutical composition that includes a biologically acceptable carrier along with an effective amount of HGFIN DNA, cDNA, RNA or protein can be used for the treatment and/or prevention of diseases associated with a lack of progenitor cell differentiation, for example leukemia and lymphoma. The specification further teaches (page 56, paragraph 0152) that these methods for treatment involve administering to the subject a pharmaceutical composition, but is silent on the in-vivo efficacy of the HGFIN polynucleotide. The specification does not show any success in treating a disease associated with a lack of progenitor cell differentiation by using the pharmaceutical composition comprising the HGFIN polynucleotide. The specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. Specifically, the specification has not taught an appropriate tested dose for humans, the amount of HGFIN gene expression necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to a pharmaceutical composition comprising an HGFIN polynucleotide, and

applicant has not enabled the pharmaceutical composition because it has not been shown that these polynucleotides are capable of functioning as to that which is being disclosed.

The instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. If the recombinant HGFIN nucleic acid were to be used in gene therapy, those of skill in the art would recognize the unpredictability of treating a disease by a method of gene therapy. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, "...the search for such combinations is a case of trial error for a given cell type" (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed nucleic acid, to select a proper dose or administration route or to determine other factors for a successful treatment. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to

engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Weterman *et al.* (IDS, 1995).

In the instant case, the claims are drawn to an isolated HGFIN polynucleotide (SEQ ID NO: 1) that encodes a HGFIN polypeptide (SEQ ID NO: 2), a vector comprising the HGFIN polynucleotide and a host cell comprising the vector.

Weterman *et al.* teach (page 74, Fig. 2, also see attached) isolation and characterization of a nucleic acid referred to as NMB (*HGFIN*, see Swiss-Prot: Q14956) which appears to have 95.7% identity to the patentably disclosed nucleic acid of interest SEQ ID NO: 1. Weterman *et al.* also teaches (page 78, 2nd column) transfection of NMB into a highly metastatic cell line (*BLM*), wherein the cells were transfected with an expression vector, pZipneo, containing NMB cDNA. Lastly, the reference teaches (page 74, Fig. 2) a protein encoded by NMB, which appears to be identical to the polypeptide (SEQ ID NO: 2) encoded by SEQ ID NO: 1. Therefore, the claimed functional limitation of a polynucleotide that encodes a HGFIN polypeptide would be an inherent property of the NMB nucleic acid taught by Weterman *et al.*. The patent office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable

differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim 2 is objected to for being dependent from a rejected base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

GARY NICKOL
PRIMARY EXAMINER